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GUEST EDITORIAL

Axillary Lymphadenectomy: A Diagnostic and Therapeutic Procedure

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The basic tenets of surgical oncology include that the surgical approach to primary operable cancer should afford maximal local control with an attempt to maximize preservation of function, have an impact on the natural history of the disease with a curative intent, and provide biologic information regarding the tumor as it relates to prognosis and efficacy of adjuvant therapy. The role and efficacy of axillary dissection for invasive breast cancer should be evaluated according to these parameters and compared to any other viable alternatives [1–4].

Long-term survival exceeds 90% in the earliest of lesions [5–7]. Survival is directly related to the size of the lesion and the involvement and number of involved axillary lymph nodes [8,9]. There is a well-described linear relationship between tumor size and nodal involvement [9]. Even the smallest of lesions, such as a T1A lesion, are associated with ~10–15% risk of axillary nodal disease [10–12]. The progression from primary tumor to nodal involvement and subsequent distant metastatic disease often takes a very orderly progression [13–17]. Tumor size is directly related to nodal involvement [9]. Ductal carcinoma in situ is rarely associated with nodal disease, [18,19] and DCIS with microinvasion has been reported to have nodal disease ~10% of the time [20]. Small invasive cancers such as the T1A are reported to have a 10–15% incidence of nodal disease [5,16]. Similar information was reported by Winchester [21] compiling >300,000 cases in the American College of Surgeons data bank and found a 15% frequency of axillary disease in the T1A lesion. Evaluation of all invasive breast cancers demonstrates ~40% of the total with involved axillary nodes and subset analysis demonstrates 29% involvement with T1 lesions and 58% with T2 lesions [22].

Quantitative progression of nodal involvement is also correlated with increasing involvement of nodal levels. In those patients with involved lymph nodes, ~60% have involvement of Level I, 22% with Levels I and II, and 17% with all three levels [13]. A patient with a single involved lymph node at Level I has an 8% chance of disease at Levels II and III, a 25% risk with two Level I nodes, and 66% with four or more involved Level I nodes. A T1 tumor with involved lymph nodes in Level I is associated with a 28.4% risk of involvement of the upper levels and T2 lesions with a 40% risk of upper level involvement. It is for this reason that a clinically suspicious axilla is fully dissected.

The intent of axillary dissection should be to remove all potentially involved lymph nodes. If clinically positive nodes are encountered, the dissection should be complete. Axillary dissection of the clinically and intraoperatively negative axilla should remove enough lymph nodes so as to be predictive that the remaining lymph nodes are also negative. A mathematical model of complete axillary dissection defines the minimum number of nodes removed per primary tumor size so as to predict with a high degree of confidence that the remaining nodes are negative. A minimum of 10 nodes needs to be removed to have a 93% predictive value (not a number the average cancer patient would find acceptable) that the remaining nodes are clear [23]. Axillary sampling achieves neither of the stated goals [24,25].

Surgical removal of involved axillary nodes may be associated with long-term survival. The 30-year follow-up study of Adair et al. [26] demonstrated 70% of T1N0 patients free of disease at 30 years and 45–50% of all patients with nodal involvement surviving 30 years. These survival data come from an era when primary operable breast cancer was treated with radical mastectomy with complete axillary dissection and was without the benefit of adjuvant therapy. Similar survival data were reported in a more recent series with 83% of Stage I breast cancer patients free of disease at the end of one decade and 79% at the end of the second decade [5].

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Involvement of one lymph node decreased the survival to 71% and 66%, respectively, and involvement of two nodes diminished survival an additional 10% at each reference point. Further support comes from the occult axillary lymph node studies where survival in the 17% of cases with axillary metastasis noted only upon serial sectioning of the nodes was similar to the node negative population [27]. It would seem that there was benefit from removal of this microscopic disease in that survival was equal to the node negative without the benefit of adjuvant therapy.

It is important to recognize that although nodal involvement diminishes survival, many of the node positive patients achieved long-term disease-free survival with surgery alone. Survival is directly related to nodal involvement, and most of the attrition is early and there is little additional fall-off as time goes on. It would be difficult to understand the concept of breast cancer as a systemic disease from its inception in light of long-term local control and disease-free survival seen with surgery alone. Similar information was reported by Haagensen [9] directly relating survival to quantitative nodal involvement and reporting long-term survival with surgery alone.

The majority of breast cancer patients do not have an involved axilla and therefore do not derive survival benefit from the procedure. There is at present no accurate preoperative assessment of the axilla so as to select for those patients with a high probability of a negative axilla. In addition, axillary recurrence is a negative prognostic event with high morbidity and mortality [28]. Axillary dissection is justified in all cases so as not to undertreat the involved axilla. It would be beneficial to have a preoperative assessment of the axilla so as to identify that group of patients with a very high probability of a negative axilla so as to potentially avoid axillary dissection in selected patients.

ASSESSMENT OF THE AXILLA

Several modalities have attempted to evaluate axillary lymph nodes prior to axillar dissection [12,29–33]. Physical examination is remarkable for the impressive inaccuracy of the clinical examination with a false negative rate of at least 25%. Danforth et al. reported on 136 patients with axillary dissections, and in those patients with a clinically negative axilla, 38% had a histologically proven disease in the nodes [22]. This is in line with other series reporting a false negative rate of physical examination at 29–38% [31].

Attempts preoperatively to evaluate the axilla have ranged from mammography to computed axial tomography and position emission tomography [34–36]. Mammography is of limited value in the assessment of axillary nodes and is accurate in only the analysis of the most clinically obvious nodes. CT scanning has been reported in a small number of patients with a positive predictive value of 89%, sensitivity of 50%, and specificity of 75%, and a negative predictive value of 20% [34]. It was concluded that although the CT scan was superior to the physical examination, it was not an accurate predictor of lymph node involvement primarily because of the low negative predictive value. Other modalities include positron emission tomography utilizing 6-fluoro-deoxyglucose metabolism [35,36]. A report of 10 patients demonstrated the primary lesion in all patients and unsuspected nodal and bony disease in 40% [35].

Intraoperative assessment of axillary nodes includes sentinel node mapping and radioimmune guided surgery [31,37,38]. Both techniques require limited surgery of the nodal basin, and early results with sentinel node mapping suggest a correlation between the sentinel node and axillary nodal status. If the positive predictive value is high, such techniques would allow selective dissection of the positive axilla.

AXILLARY RECURRENCE

The issues with expectant observation of lymph nodes include the difficulty encountered in clinical examination of the axilla and those problems associated with local and distant control of the cancer. Clinical examination of the axilla is unreliable with up to a third of involved axillary nodes not detected by standard means, which may lead to a significant delay in diagnosis. Local recurrences often lead to compressive symptoms in the axilla with impingement of vascular, lymphatic, or neural structures. Although the majority of symptoms are secondary to compression rather than direct invasion, relief of the compression is not always associated with resolution of symptoms. In addition, there is the occasional patient with inoperable isolated axillary recurrence.

Local failure after complete axillary dissection is unusual and in the range of 0–2% [33,39]. Axillary recurrence in the clinically node negative in whom the axilla is not dissected occurs in the 16–37% range. Graversen et al. [39] quantified axillary recurrences according to the number of lymph nodes removed with 19% 5-year recurrence rate in those in whom no nodes were removed, 10% in those with a limited dissection and 3% in those with more than 10 nodes removed. Similar information was reported from the NSABP B-04 with a 21.2% axillary recurrence in those with no axillary dissection, 12% if six or less nodes were removed, and 0.3% if >10 nodes were removed [33].

Axillary recurrence in breast cancer often has been

compared to a similar event in melanoma with little or no reason to support such comparison. Isolated axillary recurrence in breast cancer is a poor prognostic event [28]. Axillary nodal recurrence as the sole site of disease was reported in 21% of the group randomized to no axillary therapy in the NSABP B-04 and 85% of this group eventually manifest systemic disease [28]. The time to axillary recurrence ranged from 3 months to 134 months with a median of 14.8 months, and the time to subsequent systemic failure was a median of 17.2 months. Similar experience is noted by the authors with a 79% distant failure rate at 2 years in 42 patients who underwent completion axillary dissection after isolated axillary recurrence. All patients were free of distant disease at the time of axillary recurrence, and the initial axillary treatment was not the responsibility of the authors.

ANALYSIS OF NSABP B-04

Proponents of expectant observation of the axilla often quote NSABP B-04 as the basis of their position. The study involved 1665 patients randomized to one of three treatments: radical mastectomy, total mastectomy with radiation, and total mastectomy followed by axillary dissection only if axillary lymph nodes were later clinically positive. Isolated axillary recurrences—excluding preexisting or synchronous distant failure—were reported at 18%.

An analysis of the outcome in B-04 was reported by Harris and Osteen [40]. The original B-04 report acknowledged that 35% of the patients randomized to no axillary therapy had a limited axillary dissection, including some patients with >20 nodes removed [13]. A subsequent report related local regional failure to the extent of the axillary dissection in the group randomized to no axillary therapy. Of those who were randomized to no axillary therapy and actually had no nodes removed, 21% subsequently developed an isolated axillary recurrence. Excluded from the group of axillary recurrences were patients with either preexisting or synchronous distant failure. The analysis of Harris and Osteen [40] suggests the B-04 does not have the statistical power to prove or disprove the efficacy of axillary dissection. In order to have a 90% chance of detecting a 7% difference between the two treatment groups, 2,000 patients would have been required rather than the 550 patients assigned to each arm. In addition, the difficulty of axillary assessment is not addressed so that many patients may harbor positive nodes not detected upon routine clinical follow-up. False-negative clinical examination is reported to be ~30% so that a significant proportion of the total would have undetected axillary nodal disease.

SURVIVAL BENEFIT

There are several studies that support a survival benefit of axillary treatment. The second Guy's Hospital series randomized 253 clinical Stage I patients to radical mastectomy with axillary dissection or wide local excision with postoperative radiation to the breast and axilla [41]. At 8 years, there was a statistically significant difference in both distant recurrence and survival in the group with axillary dissection. A prospective randomized trial of axillary dissection in addition to lumpectomy and radiation was completed on 658 patients with a clinically negative axilla [42]. With a median follow-up of 54 months, there was a significant advantage in survival in the axillary dissection group with less frequent visceral, supraclavicular, and axillary recurrences also noted. Adjuvant chemotherapy was given to 11 patients in the axillary dissection group and to none in the observation group. It was the conclusion of this study that a survival benefit could be demonstrated with axillary dissection.

BIOLOGICAL SIGNIFICANCE

Axillary lymph node status remains the most accurate predictor of outcome in breast cancer. Adjuvant hormonal or chemotherapy is most often predicated upon quantitative nodal status, and chemotherapeutic protocols differ according to quantitative axillary status. Adjuvant therapy in invasive breast cancer mandates therapy of all of the patients even though the majority of patients are cured with surgery alone and the incremental change in the node negative is quite small. Axillary dissection provides information of those patients at highest risk for relapse and therefore greatest potential gain from adjuvant therapy.

SUMMARY

Axillary dissection for primary operable cancer follows the basic tenants of surgical oncology and achieves the stated goals. Local control is excellent with failure rates in the 0–2% range. Long-term and disease-free survival is improved with axillary dissection. It is often stated that axillary dissection is not required for the smallest of lesions, but the 15% risk of axillary disease with the T1A lesion would suggest otherwise. Axillary sampling would not achieve the stated goals because of the high probability of retained, potentially resectable disease in the node positive group. Axillary recurrence is associated with an unacceptably high morbidity and mortality. Although the survival is similar in the three treatment groups of NSABP B-04, the inordinately high systemic failure rate with axillary recurrence would suggest that more aggressive local control could prevent many of

these failures. After all, long-term survival free of disease is reported in many series even in patients with multiple involved nodes.

Axillary dissection also generates the most accurate prognostic variable upon which further therapeutic interventions are predicated. At present there is no other diagnostic or therapeutic approach that achieves all of these goals.

In summary the value of the axillary dissection is to provide accurate prognostic information as well as excellent local control and to improve the survival rate in the node positive group. It is hoped that in the future a diagnostic test such as PET scanning or sentinel node mapping may predict those patients with a clear axilla and therefore not require an axillary dissection.

Finally, there has yet to be a primary operable carcinoma that benefits from preservation of potentially fully resectable disease.

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